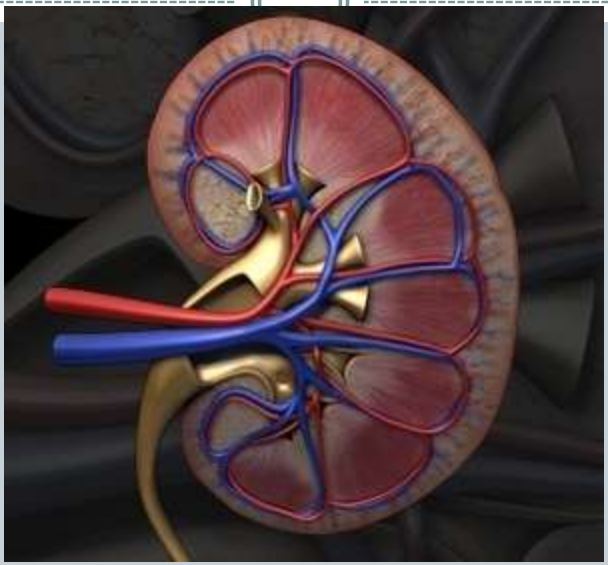
Endocrinal Manifestations of Chronic Kidney Disease



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.Impaired kidney function and chronic kidney disease (CKD) leading to kidney failure and end-stage renal disease (ESRD) is a serious medical condition associated with increased morbidity, mortality, and in particular cardiovascular disease (CVD) risk.

. CKD is associated with multiple physiological and metabolic disturbances, including hypertension, dyslipidemia and the anorexia-cachexia syndrome which are linked to poor outcomes.

. Specific hormonal, inflammatory, and nutritional-metabolic factors may play key roles in CKD development and pathogenesis.

.These include raised proinflammatory cytokines, such as interleukin-1 and −6, tumor necrosis factor, altered hepatic acute phase proteins, including reduced albumin, increased C-reactive protein, and perturbations in normal anabolic hormone responses with reduced growth hormone-insulin-like growth factor-1 axis activity.

.Others include hyperactivation of the renin-angiotensin aldosterone system (RAAS), with angiotensin II and aldosterone implicated in hypertension and the promotion of insulin resistance, and subsequent pharmacological blockade shown to improve blood pressure, metabolic control and offer reno-protective effects.

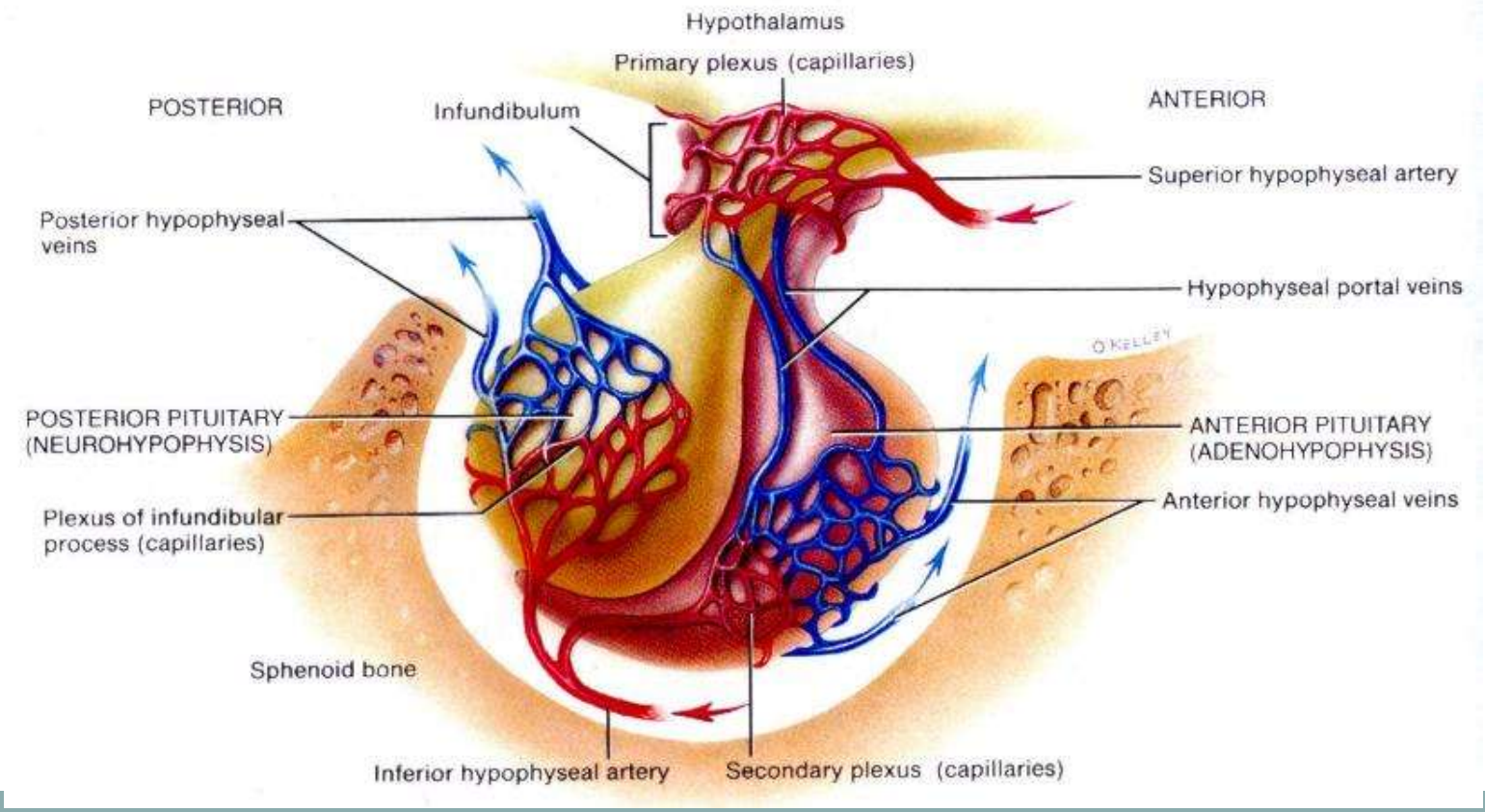
.Abnormal adipocytokine levels including leptin and adiponectin may further promote the insulin resistant, and proinflammatory state in CKD.

.Poor vitamin D status has also been associated with patient outcome and CVD risk and may indicate a role for supplementation.

Outline

1. HPG Axis abnormalities in Uremic Men
2. HPG Axis abnormalities in Uremic Women
3. Thyroid function in CKD
4. CHO and Insulin metabolism in CKD

HPG Axis abnormalities in CKD Men



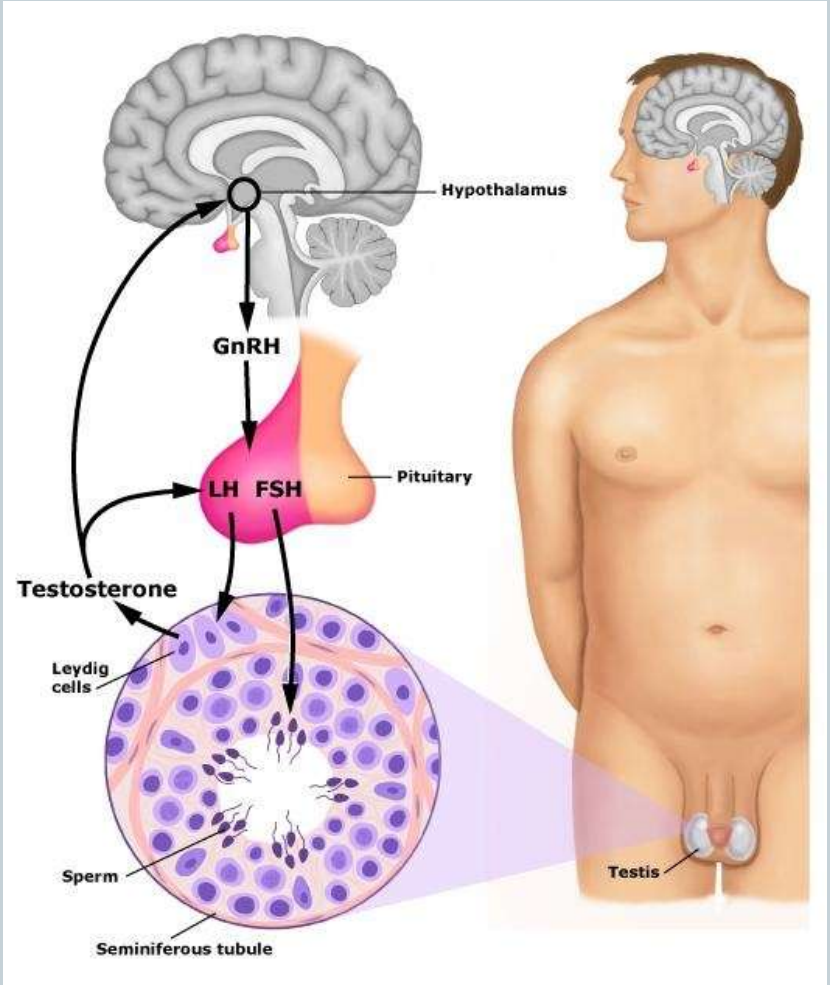
Men with CKD

- At least 50% (some studies say up to 80%) of men with CKD :
  - ED
  - ↓ libido
  - ↓ frequency of intercourse
- Improve with dialysis BUT don't normalize
- Even with transplant, ↓ libido and ED remain

HPG Axis in Uremic Men Overview

- ↓ Gonadal function
  - ↓ testosterone production
- ↓ Hypothalamic-pituitary function
  - Blunted increase in serum LH levels (but total LH increased)
  - ↓ LH secretory burst
  - Var. increase in FSH levels
  - Increased PRL levels

  Partial improvement with dialysis



Testicular Functions

- Impaired spermatogenesis and testicular damage → infertility
- Semen analysis:
  - Decreased volume of ejaculate
  - Low or complete azoospermia
  - Low percentage of motility
- Histologic analysis
  - Decreased spermatogenesis
- Pathologic analysis
  - interstitial fibrosis, calcifications in seminiferous tubules, epididymis, corpora cavernosa, atrophy of sertoli cells

Guvel S, Pourbager M, Torun D, et al. J Androl 2004;25:752-756

Testicular Function

- No hypertrophy in sertoli or leydig cells
  - Suggesting hormonal regulation defect of cells as in gonadotropin deficiency or resistance (? functional hypogonadism)
- Etiology of testicular damage in uremia clear
  - ??? Plasticizers in dialysis tubing (e.g. phthalate) potentiating the cytotoxic effects ???
  - ….but then why does dialyzing more frequently improve sexual dysfunction…

Sex Steroids

- Total and free testosterone reduced.
- Binding capacity and concentration of sex hormone binding globulin (SHBG) normal.
- Stimulation by HCG (LH like action) gives only blunted response in uremic men.
  - Possible factor blocking LH receptor in CKD
  - Reversed by transplantation
- Total plasma estrogen concentration increased .

Dunkel L. et al. Kidney Int 1997;51:777-784

Hypothalamic-Pituitary Function

- Increased LH in CKD :
  - decreased Testosterone release from leydig cells → no feedback inhibition of LH release
  - Decreased metabolic clearance rate of LH with CKD
  - In CKD, LH bursts normal but amount secreted decreased
- FSH increased in men with CKD and LH/FSH ratio increased (LH proportionally higher)
- Inhibin made by sertoli cells inhibits FSH:
  - Highest FSH in pts with most severe damage to seminiferous tubules
- High FSH poor prognostic sign for spermatogenesis recovery after transplant

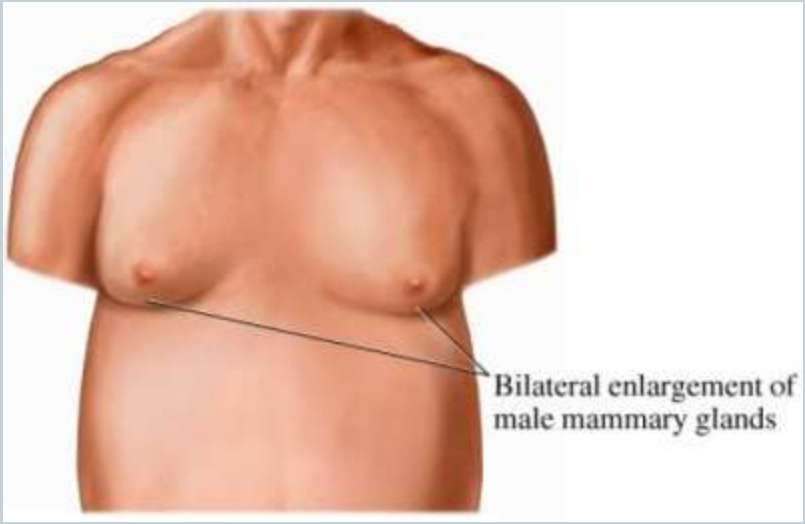
Prolactin Metabolism

- In normal men severe hyperprolactinemia results in:
  - Infertility, loss of libido, low circulating testosterone levels and **LOW LH levels**
- In CKD
  - PRL levels increased but significance unclear as **LH also INCREASED**
  - PRL secretion autonomous and resistant to normal stimulatory and suppressive measures.
    - No effect with DA (-), arginine (+), insulin induced hypoglycemia (+), or TRH (+) infusion
- Possible cause of increased PRL levels
  - Hyperparathyroidism
    - PTH infusion in nl men causes ↑ PRL
  - Zinc deficiency in CKD

Caticha O et al. J Endocrinol Invest 1996;19:441-448

Gynecomastia

- Seen in 30% of HD men
- Pathogenesis unclear
  - ? Elevated PRL levels
  - ? Increased Estrogen : Androgen ratio

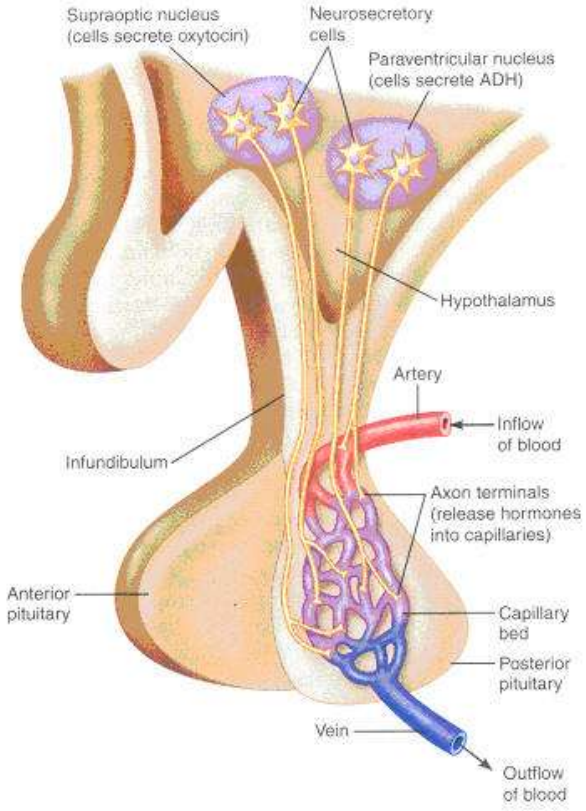


Treatment options for men

- Treatment options
  - 6 weeks hemo ….. pts show increased testosterone
    - One study showed sexual dysfunction improve from 29%-80% after 3 months of hemodialysis
  - EPO administration shown to improve sexual function
    - anemia improvement and increases in plasma testosterone levels
  - Controlling PTH levels to lower PRL
  - Viagra (60-80% response rate)
  - Clomid to increase LH and FSH
  - Vacuum device (pump)
  - Testosterone
  - Zinc replacement to raise testosterone levels
  - Transplant

Palmer et al. Adv Ren Replace Ther 2003; 10:48-60

HPG Axis abnormalities in CKD Women

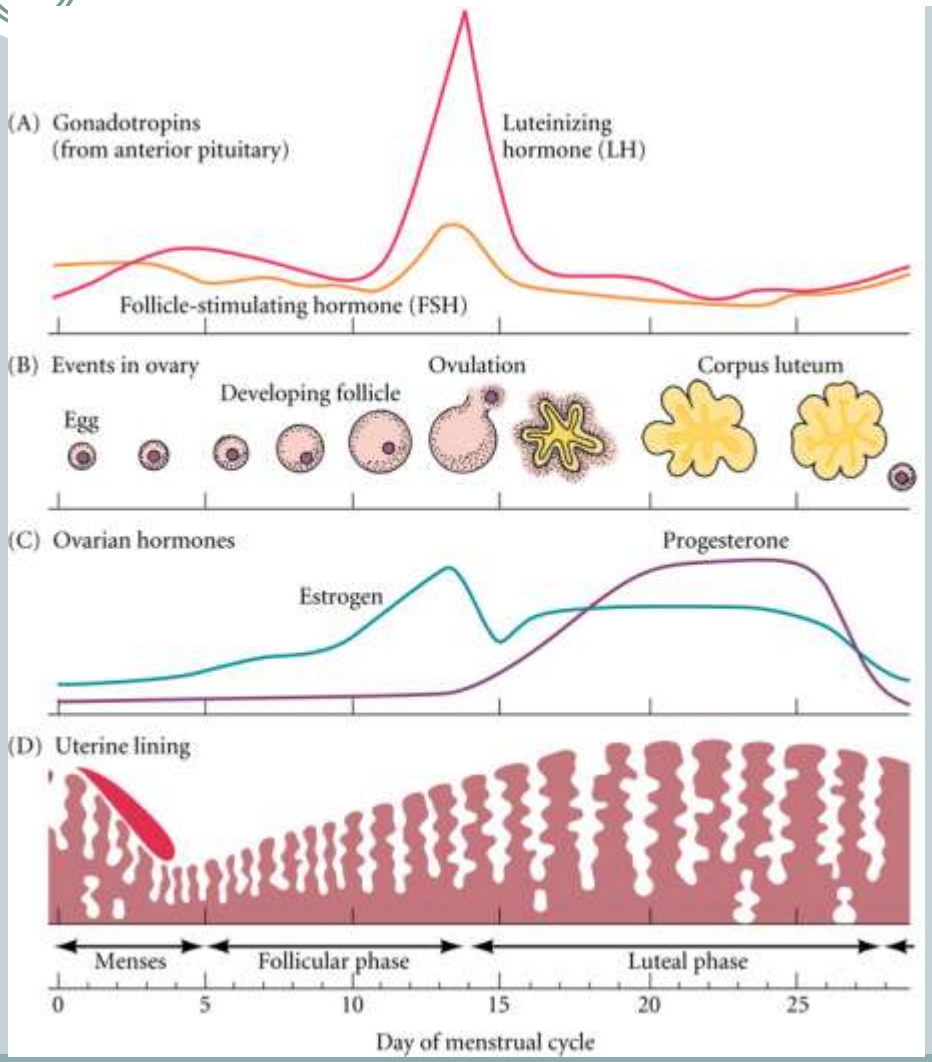


HPG Axis in CKD Women

- Major abnormalities:
  - Disturbances in menstruation, anovulation/infertility, decreased libido and reduced ability to reach orgasm.
  - Pregnancy occurs rarely BUT fetal wastage markedly increased.

Normal Menstrual Cycle Review

- Phases
  - Follicular/Proliferative phase
  - Luteal/Secretory
- Overview
  - Increase FSH sx
  - Recruitment of single ovum
  - Increase estradiol sx
  - LH surge → ovulation
  - LH stimulates corpus luteum
  - Corpus luteum sx estradiol and progesterone



Hormonal Disturbances in Uremic Premenopausal Women

- No progesterone effect on endometrium per biopsy
- No increase in basal temperature at time for ovulation (luteal phase)
- NO preovulatory peak LH and estradiol concentrations
  - Problem of estradiol positive feedback as exogenous estradiol administration does NOT stimulate LH release
  - Low dose estradiol feedback inhibition intact
- Increase in circulating endorphin levels in CKD due to reduction in opiod clearance
  - Endorphins inhibit ovulation (possibly by reducing GnRH)

Prolactin and Galactorrhea

- In CKD, women (like men) have increased PRL levels
  - Hypersecretion autonomous like men
  - Increased PRL levels impair hypothalamus and pituitary function → contribute to sexual dysfunction and galactorrhea
- Note:
  - Non CKD women with PRL producing tumors present with:
    - Amenorrhea, galactorrhea, and low gonadotropins
  - BUT…
    - CKD women treated with bromocriptine STILL have amenorrhea and galactorrhea despite Normal prolactin.

Postmenopausal Women

- Menopause occurs at earlier age than non-CKD women.
- Gonadotropin levels similar to non-CKD women of similar age.

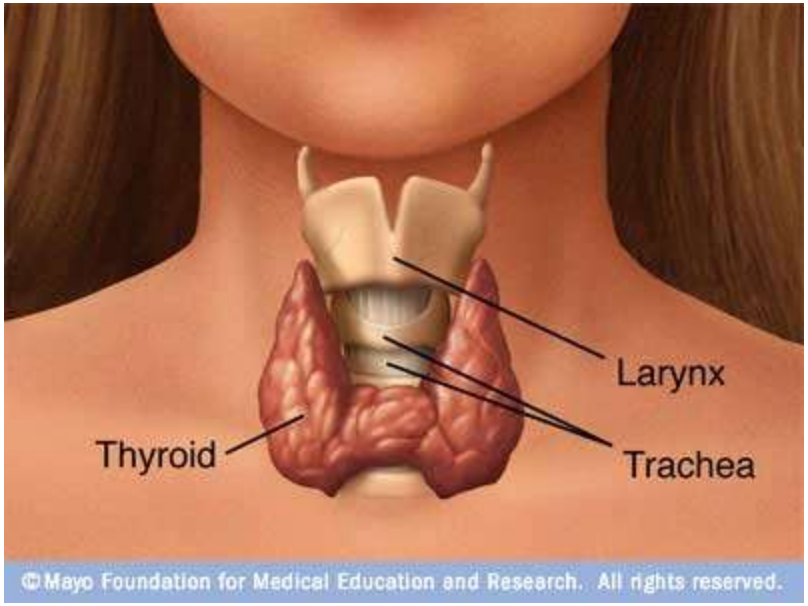
Treatment

- General: Maximize dialysis, correct anemia
- Oligo/Amenorrhea: Administer progestin 5-10 days each month to restore menses
- Restoring fertility in ESRD women discouraged due to complications
  - BUT successful pregnancy in renal transplant
- Decreased libido: No good studies;
  - possible low dose testosterone (but lots of side effects)
  - Bromocriptine (for hyper PRL)
  - Estrogen replacement (if low levels)

Treatment (cont.)

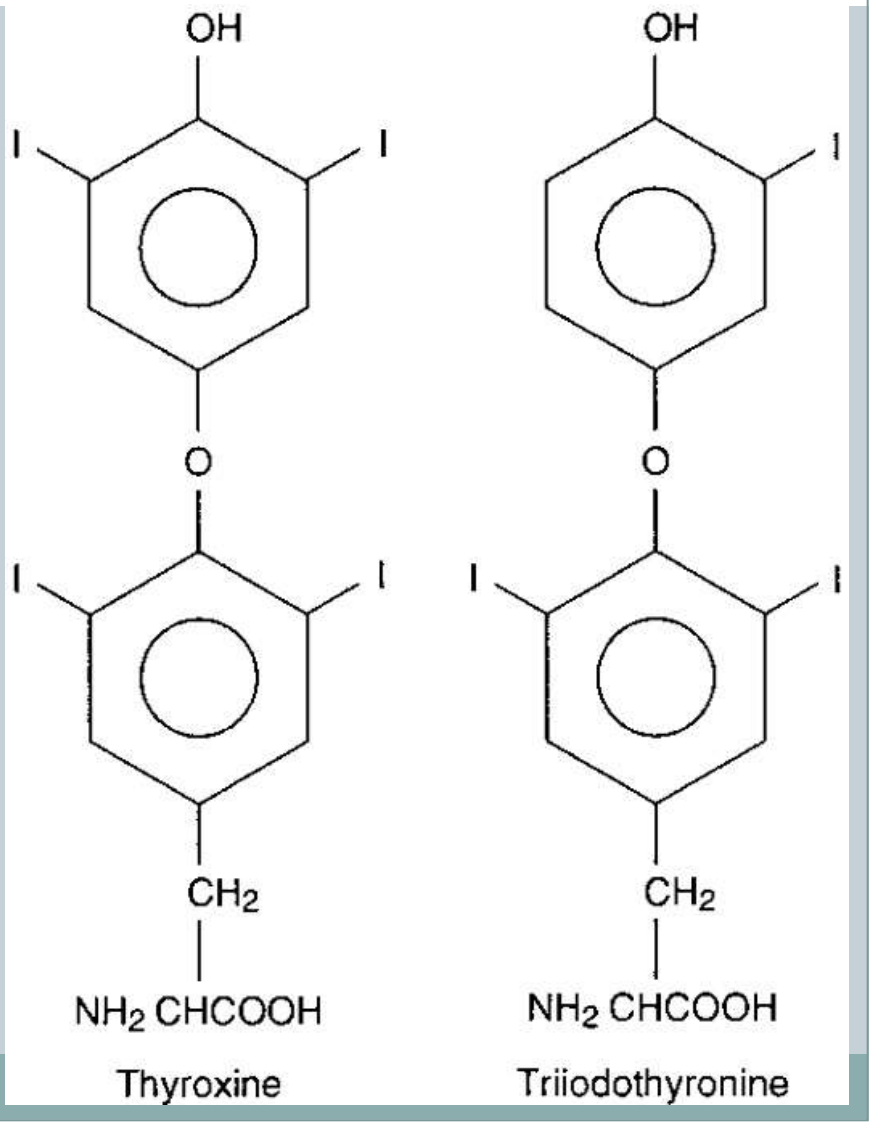
- Estrogen replacement may improve sexual function in women with low circulating estradiol levels
- Gold standard: renal transplantation

Thyroid Function in CKD



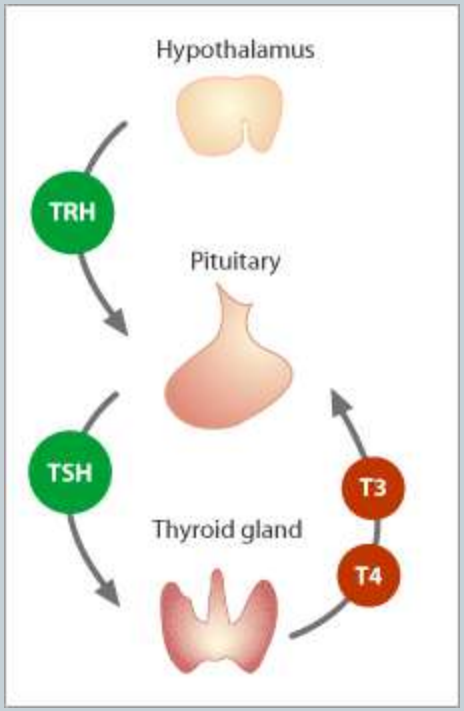
Thyroid Function Abnormalities

- ↓ total T3 due to
  - Decreased conversion from T4 .
  - Reduced protein binding to thyroid hormone binding globulin and albumin.
  - Metabolic Acidosis.
  - Circulating levels of T3 may be **increased** due to:
  - Reduced renal clearance



Thyroid Function Abnormalities (cont.)

- Normal rT3 (to differentiate from chronic illness where rT3 is enhanced).
- T4 either low or normal :
  - Heparin interferes with T4 binding to TBG (so transient ↑ after dialysis)
- Normal TSH :
  - but blunted and delayed response to TRH and attenuated during evening hours
  - Smaller amplitude of pulsatile secretion of TSH



Clinical Manifestations

- Significant overlap in findings between CKD and hypothyroidism:
  - Both have:
    - low T3
    - cold intolerance
    - puffy appearance
    - dry skin
    - lethargy
    - fatigability
    - Constipation
  - Although most uremic pts are euthyroid based on labs (normal TSH, free T4) and physical exam findings (tendon relaxation time, etc), slight increase in hypothyroidism in CKD.

Thyroid Structure Abnormalities

- Gland size:
  - Increased in CKD.
  - Mechanism unclear.
- Nodules/Carcinoma:
  - Slightly higher frequency of both
  - Mechanism unclear

Thyroid disorders

- Dialysis patients have increased serum inorganic iodide and thyroid iodine content as well as an increased incidence of enlarged thyroid gland.
- Loss of thyroid hormone through hemodialysis or peritoneal dialysis is negligible.
- Thyrotoxicosis produces hyperkinetic state. The hyperkinetic state is uncommon in dialysis patient, but fatigue,restlessness,inattention,psychiatric and emotional disturbances, and changes in seizures occur frequently which may simulate thyrotoxicosis.

Thyroid disorders

- Thyrotoxicosis leads to loss of bone mass with increased urinary excretion of CA and PO4 and increased hydoxyproline turnover with reduced levels of PTH and vitamin D.

- In dialysis patients the effect of excess thyroid hormone on bone mass is exaggerated.

- Dialysis patients develop thyrotoxicosis for the same reasons as patients without renal disease

THYROID DISOREDS

Hypothyroidism	hyperthyroidism
• Increased serum creatinine • Decreased GFR • Decreased RBF • Decreased Na reabsorption • Decreased renal ability to dilute urine • Hyponatreamia	• Decreased serum creatinine • Increased GFR • Increased RBF • Increased Na reabsorption • Resistance to rh Epo action


Education
Shift

Carbohydrate and Insulin Metabolism in CKD

Carbohydrate Metabolism

- Marked fall in insulin clearance leads to improvement in glucose tolerance
- BUT…
- Glucose control deteriorates with worsening renal function

- MUST remember BOTH concepts and treat both accordingly

Normal Renal Handling of Insulin

- Insulin (MW 6000): freely filtered
  - Renal clearance: 200 cc/min (vs. 120cc/min for NL GFR)
    - Due to glomerular filtration and tubular secretion
  - 60% clearance by glomerular filtration
  - 45% extraction from peritubular vessels
  - In tubular lumen enters proximal tubular cells by carrier-mediated endocytosis → transported in to lysosomes where metabolized into AA
    - Less than 1% of filtered insulin appears in urine

Insulin Resistance

- Uremia associated with impaired glucose metabolism:
  - Impaired tissue sensitivity .
  - Seen in mainly skeletal muscles.
  - Possible mechanism:
    - Increased hepatic gluconeogenesis.
    - Reduced hepatic/skeletal muscle uptake.
    - Impaired intracellular metabolism due to decreased glycogen synthesis, or decreased oxidation to CO_2.
    - Accumulation of nitrogenous wastes, reduced excretion of adiponectin, inflammatory cytokines and hyperparathyroidism.
- NOTE: Interestingly, actions of insulin such as K+ uptake, proteolysis inhibition, maintained in renal failure

Insulin Resistance Treatment

- Both HD and PD improve insulin resistance consistent with role of uremic toxins.
- PD restores higher insulin sensitivity than HD.

. Correction of anemia with EPO markedly increases (~50% in one study) insulin-induced glucose utilization.

- ACEI improve insulin resistance, hyperinsulinemia, glucose intolerance in CKD pts.

Insulin Resistance Treatment

- Calcitriol therapy:
  - Enhances insulin release and improves glucose tolerance.
  - Its effects independent of PTH
- PTH
  - Excess PTH may interfere with pancreatic B-Cells ability to secrete insulin
    - Possible mechanism: PTH causes increased intracellular calcium which decreases cell ATP concentration and Na-K ATPase activity

Insulin Clearance

- Decline in insulin clearance seen when GFR < 15-20cc/min
  - At this GFR, pertibular insulin unable to compensate for reduced filtration
  - NOTE: at this GFR also see concomitant decline in hepatic insulin metabolism
    - This defect reversed with adequate dialysis

PITUITARY GLAND

.CKD and dialysis alter GH, GHRH, IGF1 system such that uremic patients appear to be insensitive to GH and IGF1,may explain why acromegaly is so rare in dialysis patients.

.IGF-1 is a key peptide involved in cell growth and protein turnover acting as the primary mediator of many of the responses regulated by GH in tissues.

PITUTARY GLAND

IGF-1 action:

IGF-1 is secreted systemically (hepatic), locally and recently a muscle specific IGF isoform called *'mechano growth factor'* (MGF) has been identified. IGF-1 possesses glucose-disposal, anti-apoptotic and anti-proteolytic activities in muscle, and shares some cell signalling pathways with insulin.

PITUITARY GLAND

In pediatric renal failure and dialysis patients :the disturbance in GH/IGF_1 may lead to growth retardation .

In adult patient insensitivity to GH and IGF_1 may contribute to the catabolism and wasting that commonly occur.

PITUITARY GLAND

.Dialysis patients are resistant to the short term metabolic effects of IGF_1, (IGF_1 stimulated reduction in plasma insulin, cortisol, c-peptide and amino acid levels).

.Long term (4 to 8 years) administration of rhGH to children with CRF (achieving supranormal levels and increasing IGF_1 levels) to children with CRF, can restore linear growth . rhGH treatment may also improve muscle mass and bone density.

PITUITARY GLAND

Renal failure and dialysis do not alter the diurnal variation of cortisol or the adrenal response to ACTH.

.The dose of rhGH is higher than for patients with GH deficiency , on the order of 0.35 mg/Kg/wk (28 iu/m^2/wk) may be higher during pregnancy .

The role for rhGH in the treatment of adults on dialysis is les clear, but small short term studies showed an increase in muscle mass, handgrip strength, albumin level and increased bone turn over .

ADRENAL GLAND

.Glucocorticoids and their role in metabolic dysfunction during clinical disease has a strong research base; and they may play a role in the development of metabolic and kidney dysfunction in CKD.

.In CKD, clearance and excretion of cortisol is impaired (which may be expected), which can increase half-life and serum levels(hypercortisolemia). These activities may be potentiated in CKD by co-activation of the RAAS system and in particular aldosterone having combined negative effects including promotion of cellular insulin resistance and muscle protein loss.

Conclusions

.CKD *per se* is associated with a wide range of metabolic alterations, including disorders in the secretion of hormones and the response of target tissues, and causing endocrine dysfunctions that may contribute to worse outcomes.

. Epidemiological evidence linking alterations at the level of the hypothalamic-pituitary-gonadal axis with systemic inflammation, endothelial dysfunction, arterial stiffness, cardiovascular risk and mortality, among others.

.It is possible that these endocrine alterations are no longer innocent bystanders of uremia but instead mediators of the uremic risk.

DCDC16th ,April 2015 – Ras El Barr ,Domyat.

أنا إن قدر الإله مماتى لا ترى الشرق يرفع الرأس بعدى


Thank you!